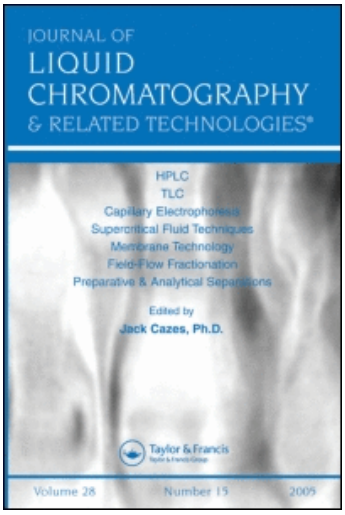

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

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Online publication date: 22 June 2010

To cite this Article Wang, Yuwen , McCaffrey, John and Norwood, Daniel L.(2008) 'Recent Advances in Headspace Gas Chromatography', Journal of Liquid Chromatography & Related Technologies, 31: 11, 1823 — 1851
To link to this Article: DOI: 10.1080/10826070802129092
URL: http://dx.doi.org/10.1080/10826070802129092

Journal of Liquid Chromatography & Related Technologies®, 31: 1823–1851, 2008

ISSN: 1082-6076 print/1520-572X online
DOI: 10.1080/10826070802129092

Recent Advances in Headspace Gas Chromatography

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Abstract: In this report, the recent and significant advances in headspace gas chromatography (HS-GC) and their resulting applications in the past five years (2002 to present) are reviewed and discussed. The discussion includes a brief overview of the recent advances in HS-GC techniques and theory, followed by examples of new applications and instrumentation for the various headspace analysis techniques. The techniques reviewed and discussed in this report include: static headspace, dynamic headspace, headspace solid phase microextraction (HS-SPME), and headspace single drop microextraction (HS-SDME). Examples of applications in environmental, clinical, forensic, biological, food, flavor and pharmaceutical analysis are provided. This report clearly indicates that research in HS-GC is very active and growing, with new applications being reported regularly.

Keywords: Dynamic headspace, Gas chromatography (GC), Single drop microextraction (SDME), Solid phase micro-extraction (SPME), Static headspace

INTRODUCTION

"Headspace analysis"–the qualitative and quantitative analysis of a gas in equilibrium with a liquid or solid sample in a closed vessel, was accomplished well before the development of gas chromatography.[1]

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Headspace gas chromatography (HS-GC) is the combination of headspace sampling and gas chromatography.[2] Since the first headspace publication in 1939,[1] headspace sampling and HS-GC[2] have been routinely employed for analysis of volatile compounds evolved from liquid and solid samples. The first documented combination of static headspace sampling (see Fig. 1a and b for Schematic diagrams) with GC was reported in 1958.[3] In 1973, dynamic headspace (i.e., purge-and-trap, see Fig. 2 for a schematic diagram) was reported.[4] In 1990, Arthur and Pawliszyn introduced the sorbent based technique, Solid Phase Microextraction (SPME)[5] and, in 1993, the technique was coupled to GC[6] (see Fig. 3a and b for schematic diagrams). In 2001, Theis et al. introduced headspace single drop microextraction (HS-SDME) in which a microliter drop of solvent is used for the extraction in the headspace[7] (see Fig. 4 for a schematic diagram).

In 2000, Luo and Pawliszyn described a membrane extraction technique for headspace vapors.[8] All these headspace sampling techniques have been used extensively in various scientific investigations and industrial applications.

The classic static headspace and dynamic headspace techniques have been developed and used for around 50 and 40 years, respectively. Many applications have been published. The relatively new technique, SPME, has a history of around 17 years, and has also been applied to numerous areas of investigation. SDME was introduced near the beginning of this decade and the number of publications is growing. Fig. 5 shows the trends of publications from 2002 to the time of this writing. As of this report, SPME headspace still represents the largest category of all headspace related publications. The number of publications of static headspace is decreasing, which may be due to the fast development of more advanced techniques (SPME and SDME). The publications of dynamic headspace applications remained flat during this period of time. Surprisingly, the number of publications of SDME increased three times since 2002 even though the total publication numbers were still small.

In this review, recent advances in the use of headspace sampling techniques coupled with GC are covered. A summary of headspace analytical techniques discussed in this review is listed in Table 1. While this review cannot be fully comprehensive, we have attempted to gather some of the most interesting current work employing headspace sampling with GC, including recent trends and anticipated future developments.

STATIC HEADSPACE GC

Static headspace GC was the earliest developed and is therefore, the most mature headspace technique. Applications have been reported in various areas and to a variety of problems. Static headspace GC is a primary tool

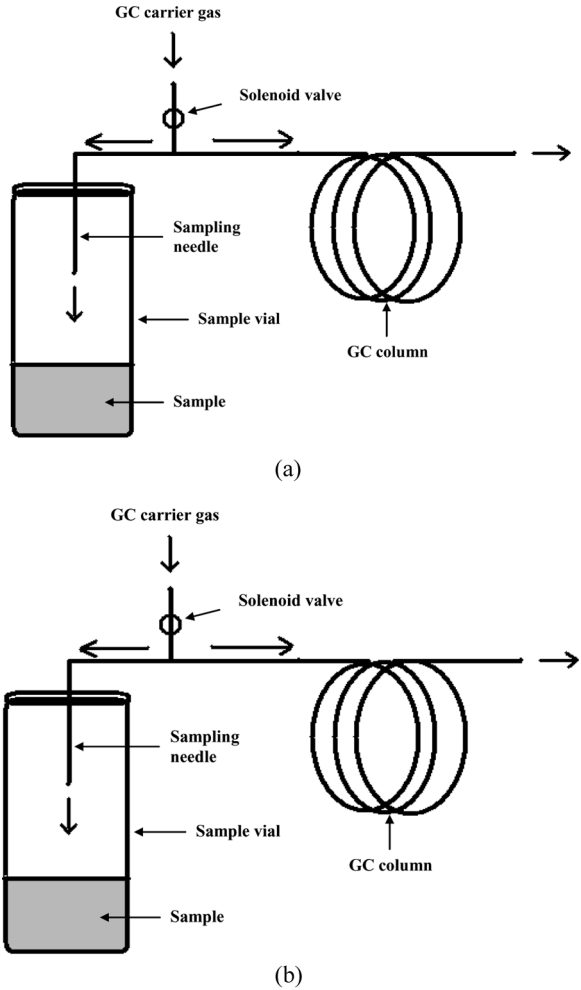


Figure 1. (a) Schematic diagram of a pressure balance static headspace system (sample pressurization). After equilibrium of the analytes is reached between the sample matrix and gas phase, the sample vial is pressurized; (b) Schematic diagram of a pressure balance static headspace system (sample introduction). The gas phase is transferred to the GC column.

for the analysis of volatile organic compounds in environmental samples, flavors and fragrances. However, because of its limited sensitivity, static headspace GC is mostly useful for applications in the high-ppb to percent concentration ranges. Several books provide excellent overviews of headspace sampling theory and the applications,[9–13] and some reviews also cover the principles and instrumentation.[14,15] In the past 5 years, static headspace GC has been increasingly applied to other fields, including

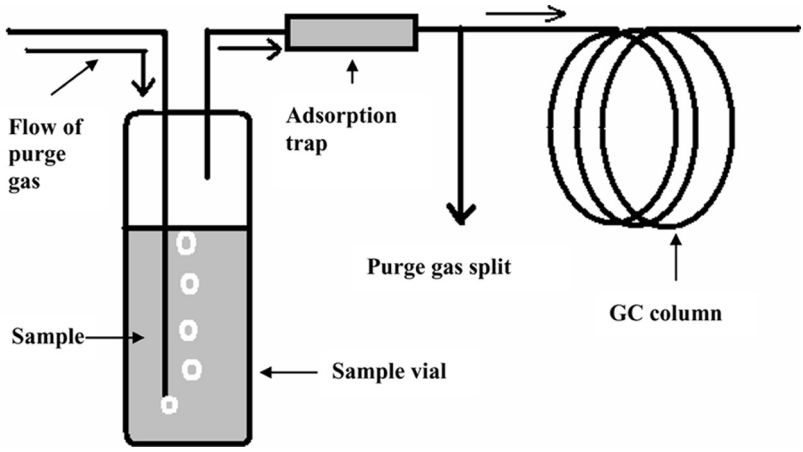
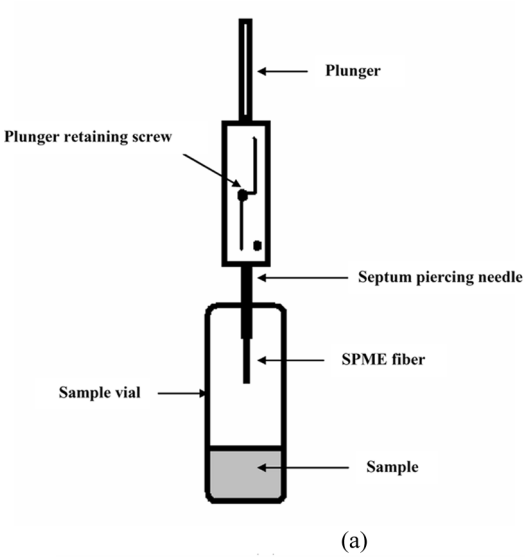


Figure 2. Schematic diagram of a dynamic headspace system. The sample is purged by an inert gas and the analytes are transferred to the adsorption trap. The trap is then heated and the analytes are desorbed from the trap and transferred to GC column.

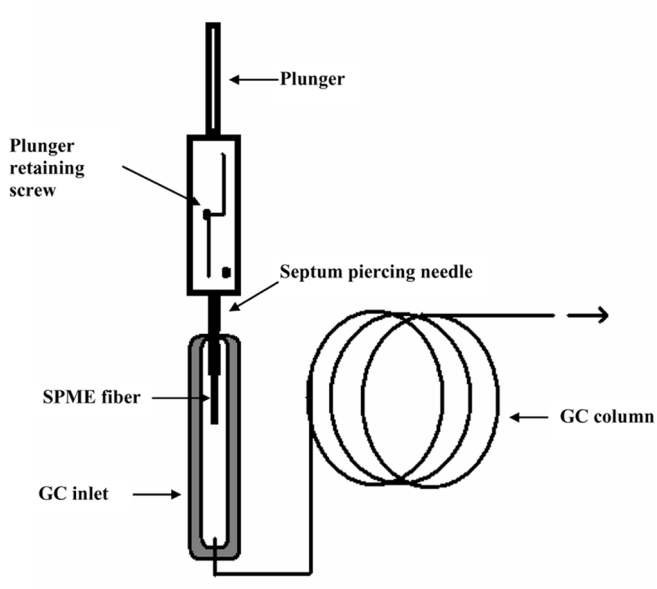
pharmaceuticals, clinical and biological analyses. Despite the rise of other headspace techniques (dynamic, SPME, SDME), as described later in this review, static headspace remains the most readily automated headspace sampling technique. As evidence of its versatility, a selection of new advances in static headspace-GC is given below.

Static headspace instrumentation is well developed and capable of being fully automated. However, the latest advancement in instrumentation comes with the introduction of a single headspace system for both static and dynamic sampling - the Teledyne Tekmar HT3 Static/Dynamic Headspace System.[16] In static headspace mode the headspace gas is sampled and directly sent to the GC, while in dynamic headspace the headspace gas is continually swept onto a trap (e.g., Tenax, activated carbon, etc.) for concentration. Once the sweeping is completed, the trap is heated and the collected analytes are sent to the GC. Another example of instrumentation development is the PerkinElmer TurboMatrix HS-110 Trap system.[17] This system is an enhanced static headspace system with a built-in trap that preconcentrates and focuses volatile compounds prior to injection into the GC.

Static headspace has been used in the pharmaceutical industry for determination of residual solvents in drug substances, excipients, and drug products. However, due to possible interactions between drug substances and the solvents tested, individual methods usually need to be developed for a specific drug substance matrix and selection of analytes. Approaches to multiple, or universal, methods for residual solvents have



(a)



(b)

Figure 3. (a) Schematic diagram of a HS-SPME system (sample extraction). Analytes are adsorbed/absorbed to the fiber coating from the headspace of sample; (b) Schematic diagram of a HS-SPME system (sample desorption). Analytes are desorbed from the fiber coating to the GC inlet.

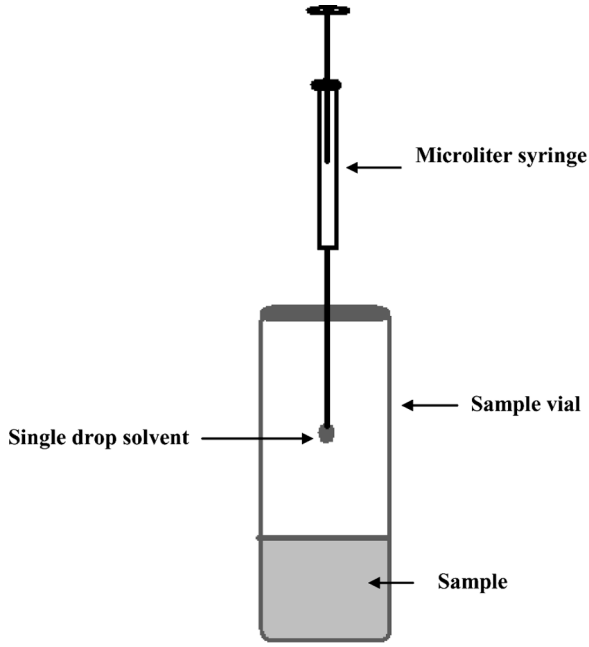


Figure 4. Schematic diagram of headspace single drop microextraction. The analytes in the sample headspace are extracted to the single drop of solvent which is suspended on the tip of a microsyringe. The single drop of solvent is transferred to GC inlet.

been proposed. For example, Tekmar reported a universal analytical method using the Tekmar HT3 headspace autosamplier with 1,3-dimethyl-2-imidazolidinone to determine residual solvents in drug substance.[18] Forty-two solvents were separated for potential quantitation in a single run. Due to the high boiling point of the diluent solvent (1,3-dimethyl-2-imidazolidinone), high boiling point residual solvents, N,N-benzyl alcohol, N-methylpyrolidone, and dimethyl sulfoxide were able to be separated in this method. The detection limits for all solvents studied are less that 2 ppm, with correlation coefficients (R^2) greater than 0.995. Rocheleau et al.[19] reported a validated general method for the determination of residual solvents in drug substances and excipients. Twenty-five analytes were included in the method, and the quantitation limits were found to be less than 50 ppm. The linearities for residual solvents tested at concentrations ranging from 0.0004 to 0.04% were found to be very good with correlation coefficients ≥ 0.999. The relative standard deviations of peak areas determined from the results of six consecutive injections at 0.0004% and 0.004% were all $<10\%$. Lee

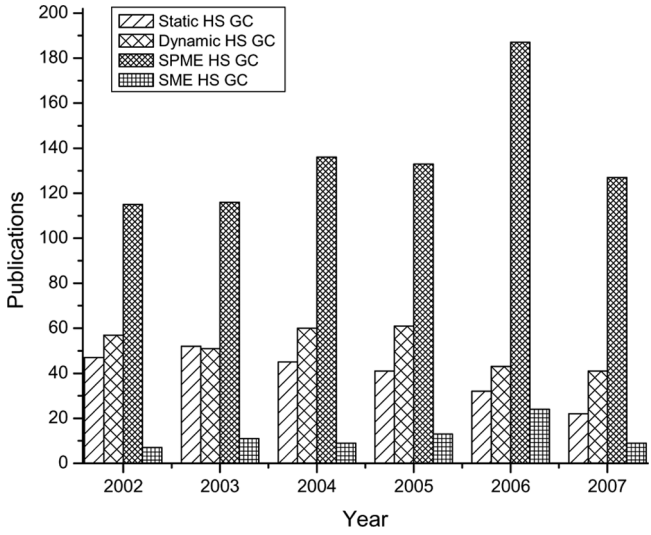


Figure 5. Numbers of publications of headspace sampling from 2002 to September, 2007.

et al.[20] reported a method for the determination of dimethyl sulfate and the methyl, ethyl, and isopropyl esters of methanesulfonic acid. Derivatization with aqueous sodium thiocyanate gave a mixture of the corresponding alkylthiocyanates and alkylisothiocyanates which, unlike the underivatised analytes, are readily analysed by GC. On-column isomerisation was determined to be negligible. These lower alkyl derivatives are sufficiently volatile for static reaction headspace analysis, and detection limits obtained by electron ionization (EI) GC-MS are below 0.05 μg/mL. The method was used to demonstrate that levels of methanesulfonic acid esters in a drug substance (a mesylate salt that had been processed using methanol and ethanol) were below 1 μg/g.

Static headspace analysis has been used in the environmental area for decades. The new applications reported in this area have focused on assessing the effectiveness of materials and processes used in the treatment of organic chemical pollutants. For example, Fourmentin et al.[21] reported a method for the determination of Henry's law constants in both the absence and presence of cyclodextrins. From this determination, the capacity of α-cyclodextrin and four β-cyclodextrins for reducing the volatility of volatile organic compounds and particularly CCl_4, chloroform and dichloromethane could be assessed. The complexation energies obtained by HS-GC are in good agreement with the results from experimental studies. This study showed the effectiveness of cyclodextrin in trapping pollutants and reducing their volatility as a method for

Table 1. Summary of headspace analytical techniques discussed in this review

Headspace technique	Acronym	Distinguishing characteristic	Comments	Selected applications and references
Static Headspace	Static HS	Analytes are extracted to a gas phase (an equilibrium may be reached between the gas phase and the sample) and the gas phase is transferred to a GC	Sensitivity is limited (low ppm to percent level). The sample could be liquid or solid.	Books and reviews [9–15] Instrumentation [16–17] Pharmaceutical [18–20] Environmental [21–24] Process chemistry [25–26] Clinical [27–28]
Dynamic Headspace	Dynamic HS	Sample, usually a liquid, is purged by an inert gas and the analytes are trapped on an adsorbent and then desorbed and transferred to a GC	Very sensitive (low ppb to ppm level). Sample is limited to liquid	Coupling with other techniques [29] Dynamic HS without standard [30] Environmental [31–39] Aroma [40–41] Forensic analysis [42]
Headspace Solid Phase Microextraction	HS-SPME	Analytes are extracted from the vapor phase of a sample by absorption in or adsorption on a thin layer of polymer coating on the solid surface of a fiber and then the analytes are thermally desorbed in a GC injector	Very sensitive (low ppb to ppm level). Sample could be gas, liquid or solid	Theory and general applications [43–46] New fibers [47–48] Pharmaceutical [49–50] Food science [51–57] Aroma [58–59] Toothpaste [60] Illicit and therapeutic drugs [61–67] Environmental [46, 68]
Headspace Single Drop Microextration	HS-SDME	Analytes are extracted in a microdrop of solvent which is suspended in the vapor phase of a sample and then the microdrop is transferred to a GC	Very sensitive (low ppb to ppm level). Sample could be gas, liquid or solid	Theory and general applications [69–94] Biomarkers [84, and 95] Environmental [89, 86, and 96]

pollution prevention. Oemuer-Oezbek and Andrea[22] reported a new headspace method for measuring Henry's law constants at varying temperatures, with subsequent determination of enthalpies of reactions for volatilization of compounds in aqueous media. The method was applied to 2-methylisoborneol, geosmin, and trans-2, cis-6-nonadienal, which are three of the major odorous compounds found in natural and drinking water. Henry's law constants for these analytes were determined at 20, 25, 32, and 39°C in distilled water, and ranged from 0.002 to 0.02, increasing with increasing temperature. Wang and Wong[23] reported a simple and rapid in-vial derivatization method for dichloroacetic and trichloroacetic acids in drinking water. The major advantages of this method are the use of acidic methanol as the derivatization agent instead of the hazardous diazomethane, and esterification is carried out in water instead of organic solvent. Dichloroacetic acid and trichloroacetic acid methyl esters produced in the reaction were determined directly by a headspace GC/ECD (Electron Capture Detection) method. The linear correlation coefficients (R^2) at concentrations ranging from 0 to 60 mg/L were determined to be 0.992 and 0.996 for dichloroacetic acid and trichloroacetic acid, respectively. Detection limits were estimated at 3 and 0.5 mg/L and recoveries were 68–103.2% for dichloroacetic acid and trichloroacetic acid, respectively. The approximation of isotherms for the vapor-phase sorption of organic compounds is a long-standing problem. This problem is especially difficult to solve in cases of natural heterogeneous sorbents (soils, sediments, aquifers, etc.), since these sorbents contain sites with different sorption activity. Breus et al.[24] reported a static headspace method for the determination of vapor sorption isotherms for twenty organic sorbates (thirteen hydrocarbons and five chlorinated hydrocarbons, seven oxygenated and two nitrogenated organic compounds) on geosorbents.

During the past five years, static headspace techniques have been increasingly used in process chemistry. For example, Chai et al.[25] reported a multiple headspace extraction for the study of process kinetics that involved volatile species. It was demonstrated that headspace GC can be used for the study of process kinetics such as chemical reactions, adsorption and desorption processes in multiple-phase systems, and diffusion processes through membranes. The results indicated that methanol formation in Kraft black liquors under isothermal conditions follows an exponential decay function. The method presented is very simple, efficient, fully automated, and is easily applied to the study of slow kinetic processes such as reaction or adsorption and desorption involving volatile species in any environmental or industrial samples with complicated matrices. Jiménez and Costa-López[26] reported a static headspace method which could be used to select solvents for reaction and extraction processes. N-alkanes, alkylbenzenes, and o-xylene were chosen as the best

solvents for transesterification of methanol and methyl acetate azeotropic mixtures with butanol using the reaction and extraction technology.

It is especially interesting that headspace methods are appearing in non-analytical science journals such as clinical journals, indicating the deep penetration of headspace techniques beyond the traditional application areas mentioned above. For example, Accorsi et al.[27] reported a method in which headspace GC was used to monitor anesthetics in urine and patient exhalation gasses. Passive samples were collected after 2.5–7 h of exposure, at the same time as post-shift urinary samples, to evaluate the individual time-weighted average exposures to sevoflurane and N_2O. The method is sensitive, and can monitor 0.1 μg/L in urine and 50 ppb in exhalation gas for sevoflurane, and 1 μg/L in urine and 80 ppb in exhalation gas for N_2O. Bouche et al.[28] reported a fully developed and validated headspace GC-MS method for quantitation of the hydrocarbons n-propane, iso-butane, and n-butane in blood samples. The method was demonstrated to be suitable for both emergency cases and forensic medicine investigations. Its practical applicability is illustrated with a forensic blood sample taken after acute inhalative intoxication with lighter fluid; case history and toxicology findings are included. Sample preparation was kept to a strict minimum and involved simply adding 2.5 μL of a liquid solution of 1,1,2-trichlorotrifluoroethane in t-butyl-methylether as an internal standard, to aliquots of blood in a capped vial. Standards were created by volumetric dilution from a gravimetrically prepared calibration gas mixture composed of 0.3% of n-propane, 0.7% of iso-butane, and 0.8% of n-butane in nitrogen. In the forensic blood sample, the following concentrations were measured: 90.0 ug/L for n-propane, 246 ug/L for iso-butane, and 846 ug/L for n-butane.

Even though static headspace GC is a well developed and mature technology, the application areas are still expanding. The main limitation of classical static headspace-GC remains its relatively limited sensitivity compared to other headspace techniques.

DYNAMIC HEADSPACE

Dynamic headspace sampling involves the passing of carrier gas through a liquid sample, followed by trapping of the volatile analytes on a sorbent, and desorption from the sorbent onto a GC. This is a well-known and well developed technique, which was used for trace (low ppb and ppt) analysis of volatile organic compounds in aqueous matrices. For dynamic headspace-GC techniques, the number of publications has declining during the past five years further suggesting the maturity of the technique. As with static headspace GC, the new advances are seen in a very wide

variety of application areas, including environmental contaminants, foods and aromas, etc. Technological advances also include new developments in data processing.

A very interesting development in dynamic headspace is its coupling with other extraction techniques. For example, Mohammadi and Alizadeh[29] reported a simple, fast and efficient dynamic headspace-organic solvent film microextraction using a new automatic device. The renewable organic films were formed inside a microsyringe barrel using the uniform and repeated movement of the syringe plunger enabled by a programmable stirring motor. The plunger speed, number of extraction cycles, and dwell time (stop time after each half round) were controlled by computer software. A theoretical treatment of the dynamic headspace-organic solvent film microextraction based on the consecutive 1st-order process is proposed. A mathematical solution for the dynamic process of mass transfer was obtained by correlating the variation of analyte concentration in the syringe volume with the plunger speed and the amount of analyte extracted. Benzene, toluene, ethylbenzene, and o-xylene were employed as model compounds to evaluate the extraction procedure, and were detected by GC. Of 1-octanol, benzyl alcohol and n-dodecane, n-dodecane proved to be the most sensitive solvent for the extraction of these analytes. Several parameters, including the syringe withdrawal rate, dwelling time, numbers of extraction cycles, sampling volume, sample temperature, and ionic strength of the solution, were studied for their effects on the extraction performance. Calibration graphs were linear at 0.5–200 ng/mL, with the detection limits between 0.18 and 0.35 ng/mL.

To analyze a sample by dynamic headspace without reference standards, Soria et al.[30] reported a multistep fractionation of a sample used to determine recovery in the dynamic headspace when reference standards are not available. Different honey volatiles were used as samples. The authors compared the fit quality of quantitative data and the recoveries by using different calculation procedures. The results for most of the honey samples are excellent which indicates the procedure can be used for these types of samples without a reference standard.

Environmental water testing is still a major part of the application of dynamic headspace. For example, Cheng and Peterkin[31] reported a procedure to analyze dimethyl sulfoxide (DMSO) in wastewater. The isotope DMSO-d_6 was used as the internal standard to ensure accuracy. The DMSO was reduced with $SnCl_2$ and measured as dimethyl sulfide (DMS) with dynamic headspace GC-MS. The method detection limit was at the sub-μg/mL level; precision, as measured by standard deviation, was better than 0.5%; and the recoveries were between 95 and 105% at the level of 2 μg/mL. The procedure could use commercial analytical instrumentation used for volatile organic compound analysis.

Field samples were tested and 12 mg/L DMSO was found in the influent to a water pollution control plant. This could potentially lead to the formation of a toxic ''canned corn'' DMS odor during treatment processes. Brown et al.[32] reported a fully automated real-time dynamic headspace sampling method for drinking water. The method is very sensitive with a detection limit less than 1.0 ug/L of trihalomethanes with acceptable accuracy and precision. Results from two online monitoring studies in chlorinated and chloraminated distribution systems are presented. Method performance, compared directly to USEPA Method 502.2, showed a very slight, but acceptable bias. This analyzer samples trihalomethanes from drinking water via pervaporation through a silicone capillary membrane contained in a gas extraction cell, followed by pre-concentration using an adsorbent trap. Trihalomethanes are subsequently desorbed from the trap onto a capillary column, separated, and detected. Zoccolillo et al.[33] reported an application of dynamic headspace to the determination of volatile chlorinated hydrocarbons from superficial snow during two Italian International Trans Antarctic Scientific Expeditions. Some volatile chlorinated compounds (chloroform; 1,1,1-trichloroethane; tetrachloromethane; 1,1,2-trichloroethylene; tetrachloroethylene) were analyzed using a highly sensitive and selective hyphenated technique consisting of a dynamic headspace injector coupled to a GC-MS. Investigated volatile chlorinated compounds were present in all analyzed snow samples with concentration levels of ng/kg. To investigate ultratrace amounts of hydrophilic compounds in water, Zhao et al.[34] reported a novel dynamic headspace method to determine trace and ultra-trace amounts of phenols by derivatization with acetic anhydride. Parameters affecting extraction efficiency (purge temperature, NaCl concentration, purge time, derivatization reagent volume), were examined. The linear range was 0.2–100 μg/L for phenol. Limits of detection were 0.08–0.15 μg/L and the %RSDs for most phenols at the 10 μg/L concentration level were $< 10\%$. Natural pool water was successfully analyzed using the proposed method. Recovery from spiked water samples was 72.9–84.2%. Salemi et al.[35] reported an automated method for the determination of trace amounts of five of the most important water odorants; 2-isopropyl-3-methoxypyrazine, 2-isobutyl-3-methoxypyrazine, 2-methylisoborneol, 2,4,6-trichloroanisole, and geosmin. Analytes were purged from a 20 mL water sample containing NaCl at room temperature in a He flow and trapped on a Tenax sorbent. The desorption step was performed with He and temperature programming; desorbed analytes were directly transferred to a GC-MS for separation and detection. The method was reproducible (relative standard deviation $< 8\%$) and linear over the calibration range (10–200 ng/L). Relative analyte recoveries from groundwater were from 80–103%; limits of detection below odor thresholds were achieved for most compounds. Martino

et al.[36] reported a dynamic headspace method to determine CH_2I_2 photolysis products in natural seawater. Their calculations show that photolysis of CH_2I_2 under natural sunlight conditions occurs predominantly between 300 and 350 nm. In seawater, calculated CH_2I_2 photolysis rates decrease quickly with depth, with 90% attenuation occurring in the top 10–25 m depending on the water clarity. The results showed that most of the CH_2I_2 was photolysed before reaching the sea surface, where this compound was depleted with respect to the underlying water column. Rosell et al.[37] reported a method for the simultaneous determination of methyl tert-butyl ether, tert-butyl alcohol, tert-butyl formate; and other gasoline additives, ethyl tert-butyl ether, tert-amyl methyl ether, diisopropyl ether, benzene, toluene, ethylbenzene, xylenes, dicyclopentadiene and trichloroethylene in soils. On the basis of US EPA method 5035 A, a fully automated closed dynamic headspace system coupled to GC-MS was optimized and demonstrated to detect μg/Kg concentrations in solid matrixes. Based on five gram samples, detection limits were 0.02–1.63 μg/Kg. The method was finally applied to provide threshold and background levels of several gasoline additives in sites not influenced by gasoline spills. The method suggests directions for the future applications on real samples in current monitoring programs at gasoline pollution risk sites, where until now little monitoring data for methyl-tert-butyl ether in soils are available. Le Pape et al.[38] reported a new extraction method using dynamic headspace for volatile compounds in algae. By using this method, seven halogenated compounds, seven aldehydes, two ketones, three alcohols, and four other compounds were identified. Among them, halogenated compounds were the most characteristic of red algae, and more particularly, iodoethane and iodopentane, which had yet been found in other seaweeds. Jochmann et al.[39] reported a method in which dynamic headspace GC is coupled with isotope ratio mass spectrometry. The method was established as a useful tool for environmental science, particularly for assessing polluted sites. It is stated that dynamic headspace is the most effective pre-concentration technique for online isotope ratio mass spectrometry, with the lowest reported method detection limits in the low μg/L range. With the goal of improving sensitivity of a fully automated GC/isotope ratio mass spectrometry method, a common available dynamic headspace system was modified. The method was evaluated for 10 aromatic compounds (benzene, toluene, p-xylene, ethylbenzene, propylbenzene, isopropylbenzene, 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, fluorobenzene) and 10 halogenated volatile organic compounds (dichloromethane, cis-1,2-dichloroethene, trans-1,2-dichloroethene, CCl_4, chloroform, 1,2-dichloroethane, trichloroethene, perchloroethene, 1,2-dibromoethane, bromoform). The dynamic headspace method demonstrated good reproducibility, linearity, and small isotopic fractionation.

Method detection limits for aromatic compounds from 0.07 to 0.35 μg/L were the lowest values ever reported for continuous-flow isotope ratio measurements using an automated system.

Aroma determination and identification from food products and plants is very important for food scientists. Beltran et al.[40] developed an analytical procedure for the quantitation of up to 39 aroma compounds in fresh tomatoes by dynamic headspace GC-MS. The method uses Tenax as adsorbent and a hexane-diethyl ether mixture as solvent for elution. The method was validated for linearity, precision (better than 20% for most compounds.), and limit of detection, which was approximately 1 ng/g. This method enabled identification of up to 30 compounds in real samples. Another example is reported by Kaack et al.[41] who determined volatile compounds emitted from elderflower. A total of 59 volatile compound were identified and quantified, and significant differences among the investigated elderflower extracts were observed for 58 compounds. Important contributors to the floral and elderflower flavor of the extracts were rose oxides, hotrienol, linalool, linalool derivatives. and α -terpineol, whereas the fruitiness and freshness of the extracts were mainly due to non-oxidized monoterpenes, aliphatic aldehydes and alcohols.

Dynamic headspace has been an important tool for forensic analysis, with a new application in this area being the origin of drugs. For example, Collins et al.[42] reported a dynamic/static headspace procedure to determine the origin of heroin seized from the North Korean merchant vessel Pong Su in Australian waters. Solvents trapped in the heroin particles during manufacture were detected by both static headspace GC-MS and purge and trap GC-MS. The solvents detected were diethyl ether and ethyl acetate, solvents typically seen in Southeast Asian heroin.

HS-SPME

HS-SPME is a solvent-free sample concentration technique for GC by which analytes are extracted from a gas by absorption in, or adsorption on, a thin polymer coating fixed to the solid surface of a fiber contained inside an injection needle or capillary. The coated fused-silica fiber is used to trap and concentrate analytes from a static or dynamic headspace process. The technique was developed in 1993 and has experienced strong growth in research interest over the past decade. The theory of HS-SPME and the general applications have been published.[43–46] Due to its high concentration efficiency, HS-SPME is generally applied to samples with concentrations in the low ppm to ppt range. HS-SPME has been used in many application areas, including pharmaceutical, environmental,

food and natural products. The following examples represent a selection of the most interesting applications.

There is a variety of SPME fibers on the market, with new fibers and fiber coating technologies still developing. For example, Farajzadeh and Matin[47] reported a new SPME fiber based on activated charcoal and polyvinyl chloride coated on silver wire. This fiber is very mechanically and thermally stable. Unlike common fiber, which is coated on fused silica, this fiber has a metallic base to which the coating adheres very strongly. An important advantage for this new fiber is that the coating can be completed in less than 30 min which compares favorably with the time to make a fiber based on fused silica. Fused silica fibers can take several days to prepare due to the many steps involved, such as conditioning in HCl, drying, deactivation, impregnation with a binder and coating. Also, the newer fiber is stable up to 250°C. It was successfully used for the analysis of n-alkanes in the gaseous phase and headspace of soil samples, after optimization of the experimental parameters, by capillary GC. Bagheri et al.[48] reported an electropolymerized aniline-based fiber coating for solid phase microextraction of phenols from water. The polyaniline film was directly electrodeposited on a Pt wire surface in H_2SO_4 solution using a cyclic voltammetry technique. The efficiency of the new coating was studied using a custom fabricated SPME device and GC with flame ionization detection, for the extraction of some phenols from the headspace of aqueous samples. The results demonstrated the homogeneity and the porous surface structure of the film, and confirmed the ability of this polymer as a suitable SPME fiber coating for trapping the selected phenols. This new coating can be prepared easily in a reproducible manner and it is rather inexpensive and stable against most of organic solvents. The polyaniline thickness can be precisely controlled by the number of cyclic voltammetry cycles. At optimum conditions, the relative standard deviations for a double distilled H_2O sample spiked with phenol and chlorophenols at ppb levels were 4.8–17% ($n = 3$) and detection limits for the studied compounds were 0.69–3.7 ng/mL.

In pharmaceutical application areas, Coran et al.[49] reported a study which used SPME headspace to determine residual cyclohexane and toluene in ketoprofen drug substance and capsules. Appropriate internal standards were necessary in order to obtain acceptable quantitative results using SPME. Deuterated analogs of cyclohexane and toluene were used as the internal standards for their study because of the similarity of affinity to the SPME fiber coating. Legrand et al.[50] reported a HS-SPME method for the quantitation of residual solvents in drugs in aqueous solution. The method is very sensitive with a detection limit of 50 pg for ethanol, 1 pg for cyclohexane, 10 pg for triethylamine, and 1 pg for pyridine. It has been demonstrated that HS-SPME GC could be

an elegant alternative for the determination of residual solvents in drugs.

HS-SPME has been applied in numerous areas of food science, and the following examples represent some of the new applications in this area. Shibamoto[51] reported a new method for the determination of acrylamide in complex matrixes, including fruits, vegetables, polymers, and particularly processed foods by HS-SPME GC. The new method can replace the commonly used HPLC and GC methods which require tedious sample preparation procedures. The method involves the trapping of acrylamide on a polymer-coated fiber directly from the headspace above a sample and then transferring the trapped acrylamide to a GC with nitrogen phosphorous detector (NPD) for analysis, This newly developed HS-SPME GC-NPD method was used to analyze acrylamide formed from polyacrylamide by thermal and photo-degradation processes. Lee et al.[52] reported HS-SPME analysis of oxidized volatiles from free fatty acids, and application for measuring hydrogen donating antioxidant activity. Volatile compounds from thermally oxidized free fatty acids at 93°C for 200 min were analyzed by HS-SPME-GC. By using this method, they found that with an increase of oxidation time, total volatiles and some individual volatiles including hexanal, 2-hexenal, 2-heptenal, 2,4-heptadienal, 2-octenal, and 2,4-decadienal increased linearly with 0.99 coefficient of determination. Qian and Burbank[53] described a SPME GC coupled with pulsed flame photometric detection method for the determination of volatile sulfur compounds in cheddar cheese. A Carboxen-PDMS SPME fiber (85 μm) was employed to extract volatile sulfur compounds from the cheese matrix. The highly reactive thiols were successfully stabilized by this procedure. An evaluation of fiber exposure time, temperature of extraction, and sample size was undertaken in order to determine effective extraction conditions. It was found that certain sulfur compounds, namely hydrogen sulfide, methanethiol, and dimethyl-trisulfide, were directly correlated with age of cheese. Plessas et al.[54] described a HS-SPME GC-MS method for the evaluation of bread aroma volatiles by using yeast immobilized on trahanas (a Greek food). The best results, including shelf-life and overall bread quality, were obtained in the case of baker's yeast immobilized on trahanas.

Another interesting application of HS-SPME is the evaluation of the quality of wine. For example, Fedrizzi et al.[55] developed a method for the quantification of light and heavy sulfur volatiles in wine by HS-SPME coupled with GC-MS. Thirteen light and heavy volatile sulfur compounds were analyzed. For the successful application of the procedure, various adsorption process parameters were optimized. In particular, the nature of the adsorptive phase, the temperature, the ionic strength of the sample solutions, and the equilibration time were considered. The best extraction conditions were obtained with

carboxen-polydimethylsiloxane-divinylbenzene (CAR-PDMS-DVB) in a 2 cm long coated fiber. This method is fast, sensitive, precise and easy to transfer to wine quality control. Gomez-Ariza et al.[56] described a two-dimensional on-line coupling method for the determination of anisoles in wine using an electron capture detector (ECD) and inductively coupled plasma mass spectrometry (ICP-MS) after SPME-GC separation. ''Cork taint,'' a musty-moldy off-odor, represents one of the most serious problems in the wine industry and 2,4,6-trichloroanisole, along with other compounds, is known to be responsible for this effect. The new HS-SPME GC-ECD and ICP-MS method can determine 2,4,6-trichloroanisole, 2,6-dichloroanisole and 2,4,6-tribromoanisole. The ''in-series'' use of ECD and ICP-MS detectors combines halogen sensitivity from ECD with the elemental selectivity of ICP-MS to confirm these compounds in complex matrixes. The optimized method demonstrated good detection limits for all the analytes, as well as high precision and sample throughput. Vlachos et al.[57] investigated matrix effects during the application of a rapid method using HS-SPME followed by GC-ECD for the analysis of 2,4,6-trichloroanisole in wine and cork soaks. The method is very sensitive (LOD = 0.177–0.368 ng/L) and repeatable (%RSD = 5.72).

Numerous applications of HS-SPME GC for aroma determination have been published. For example, the Maillard reaction of cysteine and thiamine with reducing sugars is known to be important for aroma generation both in meat and meat-like process flavourings. Cerny[58] reported a method to determine the origin of carbons in sulfur-containing aroma compounds from the Maillard reaction of xylose, cysteine and thiamine by using HS-SPME GC-MS. The volatiles produced from a solution of xylose, cysteine and thiamine, heated at 145°C during 20 min was successfully analyzed. Lusic et al.[59] reported a HS-SPME GC method to monitor the volatile profiles of lime tree, fir honeydew and sage honey in order to check the reliability of botanical origin of the samples. Several compounds belonging to the sage honey volatile profile were identified for the first time in honeys. They include tetrahydro-2,2,5,5-tetramethylfuran, 3-hexenyl ester of butanoic acid, 2-methylbenzene, maltol, methyl esters of 3-furanocarboxylic acid and benzeneacetic acid.

For the compounds which are not suitable for the HS-SPME extraction or for which the extractions are not efficient, on-fiber derivation can be used. For example, Wejnerowska et al.[60] reported a method for the determination of fluoride in toothpaste using HS-SPME followed by GC-FID. To enhance the extraction efficiency, fluoride was derivatized with trimethylchlorosilane into trimethylfluorosilane. The parameters of the SPME extraction with carboxen/polydimethylsiloxane fiber were optimized and the results were compared with the corresponding ones for a liquid-liquid extraction method. Results from toothpaste analyses using these two methods were highly correlated, indicating the potential

to use the SPME extraction as an inexpensive and solvent free alternative to the liquid-liquid extraction method.

The detection and quantitative determination of illicit and therapeutic drugs, pesticides, solvents and other potential toxins from blood, urine, hair and human tissues is still one of the most important applications in HS-SPME. In general, samples must be brought into a homogeneous aqueous solution by a suitable pretreatment such as homogenization, protein precipitation or centrifugation. Hair samples must first be digested by NaOH or extracted with an organic solvent. Pragst[61] has published an excellent and comprehensive review on the applications of SPME in analytical toxicology. Musshoff et al.[62] reported a fully automated determination of cannabinoids in hair samples using HS-SPME. After absorption of analytes for an on-fiber derivatization procedure, the fiber was placed directly into the headspace of a second vial containing N-methyl-N-trimethylsilyl-trifluroacetamide, before GC-MS analysis. The method is very sensitive with a limit of detection of 0.05 ng/mg for 9-tetrahydrocannabinal, 0.08 ng/mg for cannabidiol and 0.14 ng/mg for cannabinol. Linearity was demonstrated over a range from 0.1 to 20 ng/mg with correlation coefficients from 0.998 to 0.999. Musshoff et al.[63] also reported a fully automated procedure using alkaline hydrolysis and HS-SPME followed by on-fiber derivatization and GC-MS for the detection of amphetamine, methamphetamine, methylendioxyamphetamine, methylendioxymethamphetamine, methylendioxyethylamphetamine, methylendioxyphenylbutanamine, and methylmethylendioxyphenylbutanamine in human hair samples. In this method, 10 mg of hair is washed with deionized water, petroleum ether, and dichloromethane. After the addition of deuterated internal standard, the sample is hydrolyzed with sodium hydroxide and directly submitted to HS-SPME. After the absorption of analytes for an on-fiber derivatization procedure, the fiber is directly placed into the headspace of a second vial containing N-methyl-bis(trifluoroacetamide) before GC-MS analysis. The method is very sensitive with limits of detection between 0.01 and 0.17 ng/mg. In comparison with conventional methods of hair analysis, this fully automated HS-SPME-GC-MS procedure is substantially faster and easier to perform without using solvents. It uses minimal sample amounts and has the same degree of reproducibility. Rodriguez et al.[64] described a sensitive and solvent-free procedure for the determination of nonsteroidal acidic antiinflammatory drugs in water samples using SPME followed by on-fiber silylation of the acidic compounds and GC-MS. SPME was carried out directly over the filtered water samples using a polyacrylate fiber. Derivatization was performed by placing the SPME fiber, loaded with the extracted analytes, in the headspace of a vial containing 50 μL of N-methyl-N-(tert-butyldimethylsilyl)-trifluoroacetamide. The resulting derivatives were desorbed for three

minutes into the GC injector. The influence of several parameters on the efficiency of microextraction and derivatization steps was systematically studied. For the determined optimal conditions, an excellent linearity of over three orders of magnitude and quantification limits at the ng/L level (from 12 to 40 ng/L) were achieved. The proposed method was applied to the determination of acidic compounds in sewage water and results compared with those obtained using solid-phase extraction followed by the derivatization of the compounds in the organic extract of the solid-phase extraction cartridge. To increase the SPME extraction efficiency, Lachenmeier et al.[65] reported a headspace solid-phase dynamic extraction technique coupled with GC-MS-MS for the determination of drugs of abuse in hair samples. Solid-phase dynamic extraction is a solventless extraction technique related to SPME. The analytes are absorbed from the sample headspace directly into a hollow needle with an internal coating of polydimethylsiloxane by repeated aspirate/dispense cycles. This highly automated procedure utilizes solid-phase dynamic extraction for pre-concentration and "on-coating" derivatization as well as GC-MS-MS for selective and sensitive detection. All these steps, apart from washing and cutting of the hair samples, are performed without manual intervention on a robot-like autosampler. The headspace solid-phase dynamic extraction GC-MS-MS procedure was applied to the analysis of methadone, the trimethylsilyl derivatives of cannabinoids and the trifluoroacetyl derivatives of amphetamines and designer drugs. The method was shown to be sensitive with detection limits between 6 and 52 pg/mg hair matrix and precision between 0.4 and 7.8% by the use of an internal standard technique. Linearity was obtained from 0.1–20 ng/mg with coefficients of correlation between 0.995 and 0.999. Compared with conventional methods of hair analysis, headspace solid-phase dynamic extraction GC-MS-MS is easier to use, substantially faster, with the degree of sensitivity and reproducibility demanded in clinical and forensic toxicology. Gentili et al.[66] reported a rapid screening procedure based on HS-SPME GC-MS for the detection of many recreational drugs in hair, including cocaine which was not successfully analyzed by other techniques. By this procedure, cocaine, amphetamine, methamphetamine, methylen-dioxyamphetamine, methylen-dioxymethamphetamine, methylen-dioxyethamphetamine, N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine, ketamine, and methadone were consequently determined in human hair. The procedure is simple, rapid, required small quantities of sample and no derivatization. Good linearity was obtained over the 0.1–20.0 ng/mg range and the limit of detection was 0.7 ng/mg of hair. With respect to the emerging role of forensic science for arson investigation, Lu and Harrington[67] reported a low cost and promising on-site detection method for ignitable liquids by HS-SPME GC coupled with differential mobility spectrometry. SPME was applied as the preconcentration and

sampling method. The combined information afforded by GC and differential mobility spectrometry provided unique two-way patterns for each sample of ignitable liquid.

Many applications of HS-SPME in the environmental area have been published.[46] Zuin et al.[68] reported a very interesting method which uses HS-SPME to determine trace levels of organochlorine and organophosphorus pesticides in herbal infusions of Passiflora L. In this method, a new fiber coated with polydimethylsiloxane-poly(vinyl alcohols) was used. The method is very sensitive with a detection limit of 0.01 ng/mL for α-endosulfan and 1.5 ng/mL for malathion.

HS-SDME

HS-SDME is also called headspace solvent microextraction or headspace liquid-phase microextraction. HS-SDME has been included in two literature reviews.[69,70] In this straightforward technique, a microdrop of solvent is suspended from the tip of a conventional microsyringe and then suspended in the headspace above the sample. The original application used an 8 μL drop of *n*-octane in an aqueous sample,[71] and only a fraction of this drop was analyzed subsequently by GC. Later, a smaller drop was used (1 or 2 μL) and all of it was injected.[72,73] HS-SDME is similar to traditional headspace sampling in that volatiles are sampled from the vapors above the sample, thus avoiding interferences from the sample matrix. A variety of methods and specialized equipment are available for this purpose. In HS-SDME, the fiber used in SPME is replaced by a liquid microdrop that also can be chosen for its selectivity. The first papers appeared in 2001[74,75] and sixteen others have followed.[76–94] The range of reported analyses includes alcohols, chlorobenzenes, trihalomethanes, and BTEX (benzene, toluene, ethylbenzene, and xylenes). For headspace sampling, the boiling point of the solvent should be high to avoid significant evaporation during sampling. The total publications of HS-SDME technique is still small but increased very rapidly during the past five years. The technique has been applied to many areas including medical, environmental and other fields. Following are the some interesting examples.

Dong et al.[84] reported a HS-SDME method with simultaneous derivatization for fast determination of the diabetes biomarker, acetone in human blood samples. In this work, a simple, solvent-free and low-cost technique was developed for fast determination of acetone in blood samples, which was based on HS-SDME and simultaneous derivatization followed by GC-MS. Acetone in blood was extracted by using the microdrop of solvent containing the derivatization agent O-(2,3,4,5-pentafluorobenzyl)hydroxylamine (PFBHA). The extracted acetone

reacted with PFBHA in the microdrop, and rapidly formed acetone oxime. Finally, the derivative in the microdrop was detected by GC-MS. The parameters of HS-SDME and simultaneous derivatization were studied, and method validation was accomplished. The proposed method was tested by application to the determination of acetone in blood samples from controls and diabetic patients. The results show that HS-SDME simultaneous derivatization followed GC-MS is a simple, rapid, solvent-free and sensitive method for the determination of acetone in blood, and also a potential tool for diagnosis of diabetes. Li et al.[87] described a procedure for the determination of hexanal and heptanal in human blood with droplet derivatization by HS-SDME GC-MS. Aldehydes in blood were headspace extracted and derivatized by a suspended microdrop of solvent containing the derivatization agent O-(2,3,4,5,6-pentafluorobenzyl)hydroxylamine hydrochloride. The aldehyde oximes formed in the microdrop of solvent were analyzed by GC-MS. The method reproducibility, linearity, recovery, and detection limit were studied and the results demonstrate that the method is feasible for the determination of hexanal and heptanal in blood, which were considered lung cancer biomarkers. Due to the sample extraction and derivatization being performed in a single step, the method provided a simple, rapid, low-cost, and efficient approach to analysis of aldehydes in blood. Dong et al.[95] reported a fast method for the determination of Z-ligustilide in plasma by HS-SDME GC-MS. Z-ligustilide is an active component in Angelica sinensis which was used as medicine. The method shows good linearity (0.02–20 μg/mL, $R^2 = 0.997$), low detection limit (10 ng/mL), and good precision (%RSD < 9). The experimental results suggest that HS-SDME followed by GC/MS is a simple, sensitive, and low-cost method for the determination of Z-ligustilide in plasma, and a low-cost approach to pharmacokinetics studies of active compounds.

The HS-SDME technique was also applied to environmental analysis. For example, Li et al.[89] reported a method for the determination of volatile halocarbons in water. The method shows good sensitivity with a detection limit from 0.002 μg/L for tetrachloroethene to 0.374 μg/L for 1,1,2-trichloroethane, and the recoveries were between 82.61 to 118.97% for the investigated ten halocarbons. The method also shows good linearity in the concentration range of 0.05–50 μg/L ($R^2 > 0.9968$). It is demonstrated that HS-SDME combined GC-μECD was a useful and reliable technique for the rapid determination of volatile halocarbon compounds in water. Deng et al.[86] reported a HS-SDME method for the determination of aldehydes in water with in-drop derivatization. A hanging microliter drop of solvent containing the derivatization agent of O-2,3,4,5,6-(pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA) was shown to be an excellent extraction, concentration, and derivatization medium for headspace analysis of aldehydes by GC-MS.

Using the microdrop solvent with PFBHA, acetaldehyde, propanal, butanal, hexanal, and heptanal in water were headspace extracted and simultaneously derivatized. The formed oximes in the microdrop were analyzed by GC-MS. Compared to liquid-liquid extraction and SPME technique, HS-SDME with in-drop derivatization is a simple, rapid, convenient, and inexpensive sample technique. Deng et al.[96] developed a HS-SDME GC-MS method using simultaneous derivatization for fast determination of short-chain aliphatic amines in water samples. In the proposed method, short-chain aliphatic amines in water samples were headspace extracted and concentrated by suspending a microdrop of solvent, and the short-chain aliphatic amines extracted in the microdrop of solvent were simultaneously and rapidly reacted with pentafluorobenzaldehyde. The formed short-chain aliphatic amine derivatives were analyzed by GC-MS. The results showed that the method provided good linearity ($R^2 > 0.99$ at 5.0–500 ng/mL), low detection limit (0.6–1.1 ng/mL), and good precision (%RSD < 10). The method was further tested by its application to quantitative analysis of short-chain aliphatic amines in wastewater samples. It was demonstrated that GC-MS following HS-SDME and simultaneous derivatization is a simple, rapid and low-cost method for the determination of short-chain aliphatic amines in water.

CONCLUSIONS

Static and dynamic headspace sampling techniques combined with GC are clearly mature technologies. However, new application areas are still being reported. The available instrumentation is capable of combining both static and dynamic headspace into one system. The new advances for HS-SPME focused on both the new fibers and new application fields. From the large number of publications, we can conclude that application of the technique is still expanding, and the applications are penetrating into newer fields. HS-SDME is a relatively new sampling technique, but development trends are strong.

Headspace sampling remains one of the premier sampling technologies for use with GC. It is perhaps the most versatile of all sampling techniques available for capillary GC, with active research being conducted by numerous researchers across many areas of science.

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